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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/535,472

12/19/2005

Signe M. Christensen

22460-003US1 / 1015US2

4416

26161 7590 06/03/2008

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EXAMINER

WOLLENBERGER, LOUIS V

ART UNIT

PAPER NUMBER

1635

MAIL DATE

DELIVERY MODE

06/03/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/535,472	Applicant(s) CHRISTENSEN ET AL.	
	Examiner Louis Wollenberger	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 March 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 43-47, 54-60, 62 and 65-68 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 43-47, 54-60, 62 and 65-68 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 17 May 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>4/21/06</u> . | 6) <input checked="" type="checkbox"/> Other: <u>Notice to comply</u> . |

DETAILED ACTION

Election/Restrictions

Applicant's election of a single inventive concept in the reply filed on 3/17/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Also acknowledged are Applicant's amendments to the claims, filed 3/17/08. With entry of the amendments, claims 43-47, 54-60, 62, and 65-68 are pending and examined herein with regard to Applicant's elections therein, summarized below.

With regard to claim 43, applicant elects "A-B-C" and "2'-deoxy-erythro-pentofuranosyl."

With regard to claim 46, applicant elects "oxy-LNA" and "beta configuration."

With regard to claims 54-62, applicant elects, 4, 5, 5, 16, and 7, respectively.

With regard to claim 64, applicant elects "O-P(O)₂-O-."

With regard to claim 68, applicant elects "chemotherapeutic compounds."

Specification/Sequence Compliance

The disclosure is objected to because of the following: This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide

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Sequence And/Or Amino Acid Sequence Disclosures. The specification as filed does not comply with the requirements above, in particular 1.821(d) at least, because it contains nucleotide sequences of over 10 nucleobases each that are not identified by accompanying sequence identifiers.

For example, several sequences are set forth at pages 27-29 and 32-42 without corresponding SEQ ID NO: identifiers. This is but a sampling of the many sequences set forth in the instant application without SEQ ID NO: identifiers. Applicants are advised to review the entire application—claims, drawings, and specification—for complete compliance with the Sequence Rules.

Thus, the Examiner notes herein that the above listing of pages and figures which set forth examples in the specification of nucleotide sequences that require SEQ ID NO: is by way of illustration. In order to be fully responsive to this Office Action, Applicant should review this application in its entirety to ensure compliance with the requirements of 37 CFR 1.821 through 1.825 and to make all appropriate corrections.

Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g).

Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re*

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Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 43-47, 54-60, 62, and 65-68 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 43, 47-51, 53, 55-96 of copending Application No. 10/717,434.

Although the conflicting claims are not identical, they are not patentably distinct from each other because conflicting application 10/717434 claims an oligonucleotide having the formula A-B-C-D, wherein A represents a sequence of locked nucleotide units; B represents a sequence of non-locked nucleotide units, wherein B has a length of 4-20 nucleotide units; C represents a sequence of locked nucleotide units; and D represents a non-locked nucleotide unit or a sequence of non-locked nucleotide units. In certain embodiments the LNAs of A and C may be beta-D-oxy-LNA units; the oligo may contain phosphorothioate linkages; and B represents a sequence able to recruit RNase H.

Therefore, one of ordinary skill in the art would conclude that the invention defined in the claims at issue is anticipated by, or would have been an obvious variation of, the invention defined in a claim in the conflicting application.

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This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112 (Enablement)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43-47, 54-60, 62, and 65-68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

The claims are drawn to pharmaceutical compositions comprising LNA/DNA chimeras or gapmers in a pharmaceutically acceptable carrier.

The "pharmaceutical composition" language in combination with disclosure in the specification (page 14) recommending the use of the antisense oligonucleotide compositions for therapeutics and prophylaxis requires that these claims be evaluated to determine whether the specification teaches how to use these compositions for at least one pharmaceutical use without undue experimentation.

However, a review of the specification fails to find any commensurate representation or exemplary embodiment teaching or showing one of skill how to prevent, diagnose, alleviate, treat, or cure any disease in humans or animals using a nucleic acid of the type now claimed.

Problems related to the pharmaceutical use of antisense nucleic acids were well known in the art at the time of invention. Such problems include the inability to routinely deliver an effective concentration of a specific nucleic acid in a target cell, such that a target gene is inhibited to a degree necessary to produce a therapeutic effect.

Jen et al. (2000) *Stem Cells* 18:307-319 teach that

"One of the major limitations for the therapeutic use of AS-ODNS and ribozymes is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive." (page 313, second column, second paragraph):

Given this unpredictability, the skilled artisan would require specific guidance to practice use the claimed pharmaceutical compositions to treat one or more disorders *in vivo* in any given

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patient. That is, specific guidance would be required to teach one of skill in the art how to use the claimed compositions to produce a positive effect in a patient.

A review of the instant application fails to find exemplary disclosure illustrating the proposed use of the compositions to treat any organism, mammal, or human subject. Instead, the specification makes general statements regarding formulations, dosing, and administration (pp. 11-14, for example). Examples of *in vivo* use of the pharmaceutical compositions, working or otherwise, are not provided.

Cell culture examples are generally not predictive of *in vivo* inhibition and the methods of delivery to a cultured cell would not be applicable to delivery of oligonucleotides to any organism. Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

Given these teachings, the skilled artisan would not know *a priori* whether introduction of oligonucleotides *in vivo* by the broadly disclosed methodologies of the instant invention, would result in the oligonucleotide reaching the proper cell in a sufficient concentration and remaining for a sufficient time to provide successful inhibition of expression of a target gene. In fact, the state of the art is such that successful delivery of oligonucleotide sequences *in vivo* or *in vitro*, such that the polynucleotide or oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of using nucleic acids in therapeutic applications in any organism. The teachings of the prior art does not provide that guidance, such that the skilled artisan would be able to use

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the claimed pharmaceutical compositions in the manner disclosed to produce the intended effects of treating the disclosed diseases.

Thus, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to use the claimed invention commensurate with the claims scope.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement. Removing the “pharmaceutical” language from the instant claims would overcome this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 43-47, 54-58, and 62 are rejected under 35 U.S.C. 102(b) as being anticipated by Kurreck et al. (2002) *Nucleic Acids Res.* 30:1911-1918 (Medline edate: 4/25/02).

Claim interpretation:

The claims embrace compositions comprising antisense oligonucleotide LNA-DNA-LNA gapmers and LNA/DNA chimeras, comprising oxy-LNAs, of the type taught by Kurreck et al.

The rejection:

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Kurreck et al. taught LNA/DNA mixmers, gapmers, and end blocks, 18-nucleotides in length capable of inducing RNaseH-mediated cleavage of a complementary mRNA target (Table 1, page 1912; and pp. 1913-4). More specifically, Kurreck et al. taught 18-nucleotide LNA-DNA-LNA mixmers, gapmers, and end blocks, having first and second regions (A and C) of at least 1 to 5 oxy LNA monomers in the beta configuration flanking a third, or central, region (B) consisting of DNA and optionally 1 or 2 LNAs (see Table 1). The central DNA gap, which in certain embodiments has at least one LNA, is said to be necessary for recruitment of RNase H (page 1913-4 and 1916-7). In fact, with the exception of LNA 21, each of the oligos disclosed in Table 1 therein has RNase H-mediated mRNA cleavage activity.

While Kurreck et al. do not disclose the nature of the carrier in which the oligos are delivered from the commercial vendor (page 1912, left column, "Proligo"), absent evidence to the contrary, the buffer in which oligonucleotides are typically delivered or reconstituted (if delivered lyophilized) is a pharmaceutically acceptable carrier---e.g., Tris-HCl/EDTA, pH 7.2.

Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See *In re Ludtke* 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Accordingly, Kurreck et al. taught each and every aspect of the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 43-47, 54-60, 62, and 65-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kurreck et al. as applied to claims 43-47, 54-58, and 62 above, and further in

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view of Monia et al. (US Patent 6,884,787); Crinelli et al. (2002) *Nucleic Acids Res.* 30:2435-2443; and Wengel et al. (WO 99/14226).

Kurreck et al. are relied on for the reasons given above.

Even if Kurreck et al. did not, in fact, disclose a pharmaceutically acceptable carrier for storing or reconstituting said LNA-DNA-LNA oligonucleotides, it would certainly have been obvious at the time of invention to formulate LNA-DNA-LNA oligonucleotides of the type disclosed by Kurreck et al. in a pharmaceutically acceptable carrier in view of the disclosure of Kurreck et al. and Monia et al., who each taught that antisense gapmers, whether composed of LNAs or 2'-sugar modified nucleotides or both, are useful tools for inhibiting gene function in a cell in vivo for either research or therapeutic purposes (see page 1911 and 1917 of Kurreck et al., and col. 3, 7, 15, and 16 of Monia et al.). Thus, it was well known in the prior art to use antisense oligonucleotide, whether modified or not, for therapeutic purposes and to formulate the oligos in a manner suitable for such purposes, as in a pharmaceutically acceptable carrier.

To be clear, the fact that such oligos are formulated in a carrier deemed acceptable by the art for pharmaceutical use does not preclude the use of such compositions for in vitro diagnostic or research purposes, as many carriers used to formulate oligos for in vitro use would incidentally also be suitable for use in vivo. (Thus, while the claimed compositions may not be enabled for a pharmaceutical use, the compositions are, nevertheless, obvious given that the prior art taught methods, materials, and reasons for making compositions in carriers suitable for pharmaceutical use.)

Kurreck et al. further do not teach LNA-DNA-LNA gapmers 16 nucleotides in length, such gapmers comprising phosphorothioate linkages, or formulations thereof comprising chemotherapeutic compounds.

However, the prior art is replete with disclosures teaching and recommending the use of antisense chimeras or gapmers of various lengths, comprising a central DNA gap flanked by one or more modified or non-standard nucleotides and one or more phosphorothioates to protect the antisense oligonucleotide against nuclease degradation while preserving RNaseH activity. It is clear from the prior art that it was well known at the time of invention that LNAs, 2'-sugar modifications, and phosphorothioates could be used alone and in combination to optimize the stability, solubility, cellular uptake, and activity of antisense oligonucleotide.

Thus, with regard to claims 65-67, in addition to the disclosure of Kurreck et al. teaching the benefits and utilities of LNA-DNA-LNA gapmers, Monia et al. taught that antisense oligonucleotides may be synthesized as composite structures of two or more modified oligonucleotides and/or oligonucleotide mimetics wherein the arrangement of said nucleotides is in the form referred to in the art as "gapmers" (col. 12). It is taught that preferred modifications include phosphorothioate linkages, locked nucleic acids, and 2'-sugar modifications (cols. 8-9). It is taught that these modifications may be combined and incorporated into the same antisense compound to optimize its activity (col. 12, lines 23-35). With regard to claims 59 and 60, Monia et al. taught that antisense compounds can be anywhere from 8 to 50 nucleotides in length, preferably 12-30 nucleotides in length. Thus, for example, an oligo may be 12, 13, 14, 15, or 16 nucleotides in length

Methods and materials for making LNA-containing oligonucleotides were well known in the prior art, as evidenced by Kurreck et al., Monia et al. (col. 9, citing WO 99/14226, and col. 12, bottom bridging to 13), and Wengel et al., who taught methods for making oxy-LNAs of both alpha and beta configurations.

Thus, with regard to claims 59 and 60, absent evidence of secondary considerations, the particular length of the antisense oligonucleotide does not patentably distinguish the claimed invention from the prior art, since one of skill would reasonably anticipate LNA-DNA-LNA gapmers and chimeras of lengths in the range disclosed by the prior art to have the same general properties, varying in degree only and not in kind.

With regard to claim 68, Monia et al. taught that antisense oligonucleotides, including chimeras and gapmers, may be formulated in pharmaceutical compositions with one or more chemotherapeutic agents (col. 28, lines 1-10).

Apart from their exonuclease stabilizing properties, taught by Kurreck et al. and Monia et al., the benefits and utilities particular to LNA-containing oligonucleotides were well known in the prior art, as shown by Crinelli et al., who taught that LNAs have high binding affinities for complementary sequences, are readily soluble in aqueous environments, and can be delivered into cells using standard protocols (page 2440). Crinelli et al. also recommend using LNA-DNA-LNA gapmers, albeit for a purposed different from Kurreck et al. and Monia et al.

Accordingly, the prior art is replete with disclosure teaching and recommending the use of LNA/DNA gapmers and chimeras of the type now claimed, as well as countless other varieties in antisense oligonucleotides of various lengths from about 8 to 50 bases. The benefits and utilities of such LNA-containing compounds is clearly set forth in the prior art, as represented by

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the references cited herein. Methods and materials for making and using a variety of LNA-DNA-LNA gapmers were widely available, and the level of skill in the art for making and testing such constructs was high. Several exemplary embodiments were available (Kurreck et al. and Crinnelli et al.), adequately attesting to the benefits and utilities. Monia et al. clearly show that multiple sugar-phosphate backbone modifications may be incorporated into the end-flanking regions of an oligo to improve its properties. Thus, one of skill would have had a reasonable expectation of success and ample reason to make and use LNA/DNA compositions of the type now claimed.

Accordingly, in the absent of convincing evidence to the contrary, the instantly claimed invention would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louis Wollenberger/
Examiner, Art Unit 1635
May 29, 2008